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TREATMENT OF NON-INFLAMMATORY AND NON-INFECTIOUS BOWEL DISORDERS
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- (57) Claim

1. A method of treating non-specific bowel disorders as herein defined comprising the step of dosing a patient suffering therefrom with an antibiotic agent, being a salicylic acid derivative.

2. A method according to claim 1 wherein the disorder is any one of constipation, non-ulcer dyspepsia, gastro-oesophageal reflux with or without oesophagitis, and diverticular disease, and the antibiotic agent comprises any one of sulfasalazine, 5-aminosalicylic acid, 4-aminosalicylic acid, and benzalazine, or a combination of any two or more of those agents.

3. A method according to claim 1 wherein the disorder is irritable bowel syndrome and the antibiotic agent is any one of 5-aminosalicylic acid, 4-aminosalicylic acid, and benzalazine, or a combination of any two or more of those agents.

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(21) International Application Number: PCT/AU91/00482 (22) International Filing Date: 17 October 1991 (17.10.91) (30) Priority data: PK 2950 22 October 1990 (22.10.90) AU (71)(72) Applicant and Inventor: BORODY, Thomas, Julius [AU/AU]; 144 Great North Road, Five Dock, NSW 2046 (AU). (74) Agent: CARTER SMITH & BEADLE; PO Box 296, Five Dock, NSW 2046 (AU). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.	Published With international search report. 652 191	
(54) Title: TREATMENT OF NON-INFLAMMATORY AND NON-INFECTIOUS BOWEL DISORDERS (57) Abstract A medicine for treating non-inflammatory and non-infectious bowel disorders, such as irritable bowel syndrome, constipation, non-ulcer dyspepsia, gastro-oesophageal reflux with or without oesophagitis, and diverticular disease, comprising a salicylic acid derivative, such as any one of sulfasalazine, 5-aminosalicylic acid, 4-aminosalicylic acid, and benzalazine, or a combination of any two or more thereof. The treatment of those disorders comprises taking the medicine by mouth to provide a dosage rate of the salicylic acid derivative of from 200 mg to 18 g per day.		

TREATMENT OF NON-INFLAMMATORY AND NON-INFECTIOUS BOWEL DISORDERS

TECHNICAL FIELD

This invention relates to the production and use of therapeutic agents for the treatment of certain bowel disorders, namely disorders arising from unknown or non-obvious causes, which are unaccompanied by inflammation and are not due to detectable infection by known pathogenic organisms. Such disorders are referred to as non-specific bowel disorders hereinafter, and may be distinguished from specific bowel disorders having a diagnosable cause which may be treated by appropriate medication or surgery. Typical non-specific bowel disorders are irritable bowel syndrome (IBS), chronic constipation, non-ulcer dyspepsia (NUD), gastro-oesophageal reflux with or without oesophagitis (GOR), and diverticular disease.

BACKGROUND ART

The human large bowel (colon), and to a lesser extent the small bowel, contain large concentrations of various enteric bacteria. They may range in concentration from between 10^2 to 10^7 per cubic centimetre in the small bowel and up to 10^{14} per cubic centimetre in the large bowel. When the bacteria are non-pathogenic, then the bowel produces no symptoms in the body.

On the other hand when the normal bowel flora is invaded or joined by pathogenic bacterial strains which may colonise the bowel and remain there long-term, chronic illness can result.

The local effects of abnormal bowel flora may include abdominal cramps caused by colonic or small bowel contraction, distension caused by either fluid or gas accumulation, diarrhoea caused by inadequate fluid absorption or excessive secretion, or constipation by abnormal motility patterns and excessive absorption of water. Severe local effects of abnormal bowel flora can include microscopic or collagenous colitis, ulcerative colitis, Crohn's disease and diverticulosis. Some of these effects are caused by local toxins, others by invasion of bacteria into the bowel lining and in others, the mechanisms are unknown.

When obvious, visible or microscopic colitis is present, it is known that beneficial clinical effects can be obtained from well known anti-bacterial drugs derived from salicylic acid, such as sulfasalazine (prepared by coupling 2-sulfanilamidopyridine with salicylic acid), 4-aminosalicylic acid, 5-aminosalicylic acid, and benzalazine.

When there are no visible abnormalities detectable in the colon and when stool tests, histology and blood tests are negative, yet patients still complain of symptoms referable to the colon, a diagnosis of IBS will often be made. Some 10-25% of the Western population suffer with this disorder which has also been termed spastic or irritable colon, unstable colon, colonic neurosis, spastic colitis or mucus colitis. In the classic case, there is a triad of symptoms including lower abdominal pain relieved by defecation, alternating constipation and diarrhoea and the passage of small calibre stools. Abdominal distension, flatulence or wind are also frequently present, as is passage of mucus as well as the sensation of incomplete evacuation. All these symptoms are present in the absence of demonstrable organic disease.

The pathogenesis of IBS has hitherto been unknown. Emotional disturbance, fibre deficiency, purgative abuse and food intolerance have all been implicated but not proven nor well demonstrated. Evidence for infection or autoimmunity is lacking. Conventional treatments for IBS have been unsatisfactory, as instanced by the very number of therapies that have, from time to time, been recommended or trialled. These have ranged from psychotherapy and dietary regimes to medication by antispasmodic agents, anticholinergic agents, barbiturates, antidepressants, bulking agents, dopamine antagonists, laxatives, opioids, and tranquillisers; all without signal success. There is no evidence that cure is possible.

IBS is one of the most common of the gastrointestinal illnesses, and though not life-threatening, causes great distress to those severely afflicted and brings a feeling of frustration and helplessness to the physicians attempting to treat it.

DISCLOSURE OF THE INVENTION

The present invention arose from observations by the applicant that treatments of patients for other complaints requiring the administration of antibiotics appeared sometimes to produce beneficial results in respect of IBS and other non-specific bowel disorders. This led to the hypothesis that as yet unproven and undocumented bowel flora alterations or infection by mildly pathogenic bacteria constitutes the mechanism which underlines the pathogenesis of non-specific bowel disorders. Having postulated infection as being the cause of irritable bowel syndrome and the other above-mentioned enteric afflictions, the applicant conducted clinical trials which have shown that antibiotic agents derived from salicylic acid, such as sulfasalazine,

5-aminosalicylic acid compounds, 4-aminosalicylic compounds and benzalazine are capable of suppressing the symptoms in most patients provided the appropriate dose is administered.

The invention consists in a method of treating non-specific bowel disorders as herein defined comprising the step of dosing a patient suffering therefrom with an antibiotic agent, being a salicylic acid derivative.

In preferred embodiments the salicylic acid derivative is one of the group comprising sulfasalazine, the aminosalicylic compounds, including 5-aminosalicylic acid (5-ASA) and 4-aminosalicylic acid (4-ASA), and benzalazine. Furthermore the compound chosen may be related, with advantage, to the particular disorder involved. Specifically, any of the foregoing group may be used in relation to constipation, NUD, GOR or diverticular disease, whereas only the aminosalicylic compounds and benzalazine are appropriate for IBS.

In each case the antibiotic may be used in a manner similar to its use for the treatment of inflammatory bowel disease.

Thus the active ingredient may be incorporated with a pharmaceutically acceptable excipient in tablets or capsules. The

capsules or tablets may be taken once at night, twice daily or three or more times daily, in dosages ranging from 200mg through to 18 grams per day. Sulfasalazine is usually administered in tablet form in a dosage of from 500mg per day to 18 grams per day in divided doses. 5-ASA or
5 its various recently available new formulations and substitutions may be used in similar doses but starting at 250mg per day. All the 5-amino salicylic acid agents have to be prepared in such a way that they are released in the distal small bowel. This requires the agent to be furnished with an enteric coating or provided in an enteric coated
10 release capsule. If 5-ASA is released in the upper small bowel and is absorbed to any extent, then it is secreted in the kidney and causes kidney damage because of crystal formation. Suitably coated or encapsulated products are already available for other purposes, for example those marketed under the names olsalazine, salazopyrin or
15 Mesasal.

As a general rule for long term therapy the dosage will commence at a low level and build up to the desired full amount over a few weeks, and the invention extends to multiple packages of individual dosage units to be taken in sequence to provide such a gradual build up.

20 From the foregoing it will be appreciated that a completely new use has been discovered for these antibiotics in an area where previously there has been no known effective treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

25 Figure 1 is a tabulation of the symptoms and their severity of a group of patients as at the commencement of a clinical trial of the invention.

Figures 2, 3 and 4 are graphical representations of selected results of the said clinical trial.

BEST MODE OF CARRYING OUT THE INVENTION

5 The best mode of carrying out the invention known to the applicant may be readily appreciated from the following description of two experimental case studies and subsequent clinical trials prompted by the apparent success of those cases.

INDIVIDUAL CASE STUDIES

Example 1.

10 A 31 year old nursing sister (HB) was investigated for chronic abdominal pain and frequent (2-6/day) loose motions with occasional constipation. Stool cultures, large and small biopsy, small bowel enema X-ray, full blood count and multiple biochemical tests revealed no abnormalities. In spite of use of added fibre, food exclusion diets and
15 antispasmodics, the symptoms essentially continued. Introduction of sulfasalazine (Salazopyrin-EN) in a dose of 1 g. b.d. resulted in abolition of pain and reversal of loose motions to formed stools. Withdrawal of therapy brought on recrudescence of original symptoms. Recommencement of sulfasalazine again brought prompt relief. The
20 patient continued to obtain the relief at 5 months follow-up. She was then changed to 5-ASA therapy (utilising the medication marketed as Dipentum) and has been able to continue with the same relief suppression for over a year and a half.

Example 2

A 42 year old female sales representative (LA) presented with lower, and occasionally generalised, abdominal cramping together with predominantly loose motions. In spite of extensive gastrointestinal investigations no organic cause was found. Commencement of dosing with sulfasalazine 1g. b.d. was accompanied by relief of almost all symptoms within 4-5 days. At 3 weeks, however, the patient developed a pronounced rash and treatment was withdrawn. 5-ASA (Dipentum) was not immediately available. Symptoms recurred. When 5-ASA was commenced at a dose of 2 tablets twice daily, the pain and loose motions again abated.

5-ASA has also been used successfully to treat non-ulcer dyspepsia in a number of patients. The dosage commenced at 250mg per day and is increased to 1g a day in the usual situation. At weeks 3-6 the effects commence with patients noticing reduction in reflux symptoms and upper GI tract bloating, eructation and burning. Similarly, chronic constipation is controlled by sulfasalazine in doses mentioned above and by the aminosalicylic acid compounds in the majority of patients in the doses described.

CLINICAL TRIAL

Patients and Method

The study was carried out on patients referred by general practitioners to a Medical Centre for Digestive Diseases, for colonoscopic evaluation of abdominal discomfort and bowel disturbances severe enough to warrant further investigation. All patients gave

informed consent to take part in the trial, which was conducted in accordance with the Revised Declaration of Helsinki.

Patients with the clinical diagnosis of IBS were offered entry into the trial if their symptom complex satisfied the Manning criteria and
5 complied with the exclusion criteria.

Exclusion criteria were:

- i colonoscopic abnormalities eg. visible colitis, polyps, carcinoma or diverticulosis;
- 10 ii histological abnormalities eg. collagenous or microscopic colitis;
- iii coagulopathy;
- iv pregnancy or lactation;
- v significant clinical or laboratory evidence of pulmonary, hepatic or renal disease or dysfunction;
- 15 vi sensitivity to salicylates; and
- vii need for non-steroidal anti-inflammatory drugs, steroids, anti-coagulants or antispasmodic agents.

The study was an open-label, single-institution, unblinded prospective pilot trial aimed at establishing whether a controlled double-
20 blind trial is warranted.

Medication

A 5-ASA formulation, namely olsalazine, (DIPENTUM; KABI-PHARMACIA) was used in the form of 250mg capsules. To reduce side effects the olsalazine was administered in a stepwise manner from 250mg b.d. in week 1, 500mg b.d. in week 2, to 750mg b.d. by week 3 and onwards. The dosage was maintained at 750mg b.d. for 6 weeks. Those patients unable to tolerate the 750mg b.d. dose were maintained on the highest dose tolerated.

Symptom assessment

The severity of symptoms was assessed by the use of a visual analog scale at entry into the trial, at 5 weeks, at termination of trial (8 weeks) and at a 12 week follow-up consultation. The analog scale consisted of a line marked by numbers at equal intervals from 0 to 10. Zero indicated absence of symptoms while 10 represented symptoms severe enough to interfere with work or requiring medication. Assessed symptoms included abdominal pain/discomfort, constipation, diarrhoea, abdominal distension and flatulence. Symptom scores were tabulated and statistical analysis carried out using Students t-test.

Results

Of 26 patients enrolled in the study, data from 23 who completed the entire trial was available for evaluation. One patient terminated the trial prematurely due to excessive headaches, while 2 failed to return at appropriate intervals for symptom follow-up. Included were 8 males and 15 females ranging in age from 24 to 74 years (average = 44.3 years).

Estimated duration of IBS symptoms ranged from 3 to 35 years, the average being 10.2 years.

Patients' initial characteristics are summarised in Figure 1. Frequency and severity of the five evaluated symptoms at entry into the trial can be obtained from the listed visual analog scores. Most patients appeared to single out a dominant symptom by assigning higher scores.

Symptom improvement

In a global assessment of their symptomatology most patients noted improvements in their dominant symptoms. Four patients of the 23 reported no appreciable change in their chief symptoms of pain (2) and constipation (2). The other nineteen patients reported a mean global improvement of 62% at 8 weeks. Abdominal pain, in particular, was significantly reduced. This was so whether the pain was diffuse, lower abdominal, left-iliac-fossa or left or right-upper-quadrant in location. Both diarrhoea and constipation also significantly improved towards normality. Flatulence and bloating symptoms showed lesser, sporadic improvement.

a. ABDOMINAL PAIN: Maximal improvement in pain scores occurred at 8 weeks. The initial score of 6.25 ± 1.74 (SD) fell to 2.55 ± 1.47 ($p < 0.005$). However, by week 12 the score returned to 5.7 ± 1.69 , being 91% of the pain score at entry.

b. DIARRHOEA: Significant reduction in the diarrhoea score was noted at both the 5 and 8 week consultation. The change in symptom score fell from 6.77 ± 1.69 (SD) at entry

to 2.35 ± 1.06 at 5 weeks and to 2.11 ± 0.60 at 8 weeks ($p < 0.005$). The score rose to 4.18 ± 1.33 by 12 weeks.

- 5 c. CONSTIPATION: Significant improvement was also noted in the symptom scores for constipation. Baseline severity score reached its nadir at 8 weeks falling from 6.1 ± 1.60 (SD) to 2.3 ± 0.48 ($P < 0.005$). The score rose again to pre-therapy values - 5.9 ± 1.99 - by the 12th week.
- 10 d. BLOATING/FLATULENCE: No significant reduction was found for these two symptoms on an overall assessment. In individual cases, however, occasional marked improvement occurred.

15 The above described results are shown in graphical form in Figures 2, 3 and 4, which represent the symptoms of abdominal pain, diarrhoea and constipation respectively, as assessed at intervals before, during and after treatment with 5-aminosalicylic acid (olsalazine). Not all patients experienced all three symptoms, the number of patients experiencing each symptom being indicated by the number n in each figure.

20 When asked if they would choose to take the medication on a long term basis 61% of patients expressed the desire to do so. Reasons for not wanting to continue medication included excessive intake of medication (6 capsules per day) or inadequate relief of symptoms for the therapy taken. Several patients specifically indicated that of the numerous therapies tried previously, olsalazine was the first

25 to really improve their symptoms.

5 Six patients have continued to take olsalazine for between 8 and 21 months for the symptoms of pain, constipation or diarrhoea. Symptom control continued with maintenance therapy. Withdrawal of treatment resulted in recrudescence of symptoms which could again be suppressed by recommencement of olsalazine.

Adverse Effects

10 Headache and nausea were recorded as the only discernible side effects of this slow, step-wise dose regimen. This occurred in four patients. No allergic reactions occurred. In one patient with constipation loose to normal motions were noted at a dose of 250 mg b.d., at which level the patient was therefore maintained.

CLAIMS

1. A method of treating non-specific bowel disorders as herein defined comprising the step of dosing a patient suffering therefrom with an antibiotic agent, being a salicylic acid derivative.

5 2. A method according to claim 1 wherein the disorder is any one of constipation, non-ulcer dyspepsia, gastro-oesophageal reflux with or without oesophagitis, and diverticular disease, and the antibiotic agent comprises any one of sulfasalazine, 5-aminosalicylic acid, 4-aminosalicylic acid, and benzalazine, or a combination of any two or
10 more of those agents.

3. A method according to claim 1 wherein the disorder is irritable bowel syndrome and the antibiotic agent is any one of 5-aminosalicylic acid, 4-aminosalicylic acid, and benzalazine, or a combination of any two or more of those agents.

15 4. A method according to claim 2 wherein the agent is sulfasalazine and the dosage rate is within the range of from 200mg to 18g per day.

20 5. A method according to claim 2 wherein the agent is 5-aminosalicylic acid, 4-aminosalicylic acid or a combination thereof and the dosage rate is within the range of from 250mg to 10g per day.

6. A method according to claim 3 wherein the dosage rate is from 250mg to 10g per day.

7. A method according to any one of the preceding claims wherein the dosage rate commences at a low commencement rate and is escalated over time through at least one larger intermediate rate to a still larger final rate.

- 5 8. A method of treating non-specific bowel disorders as herein defined substantially as hereinbefore described.

DATED: 22 June 1994

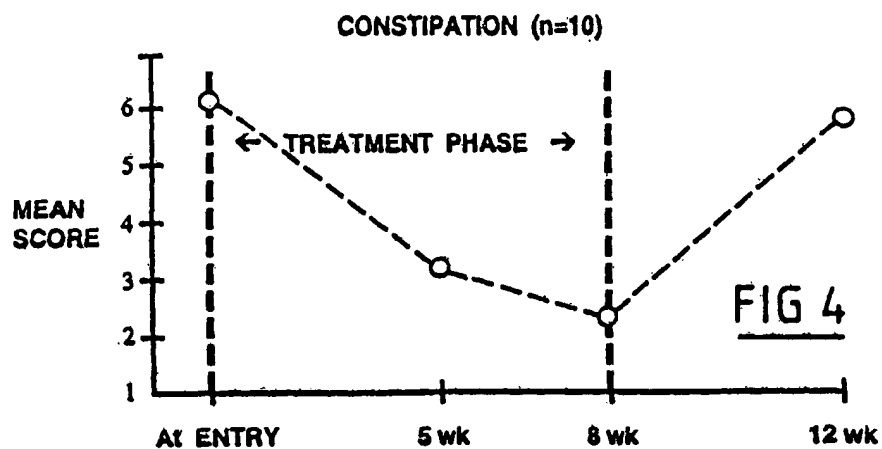
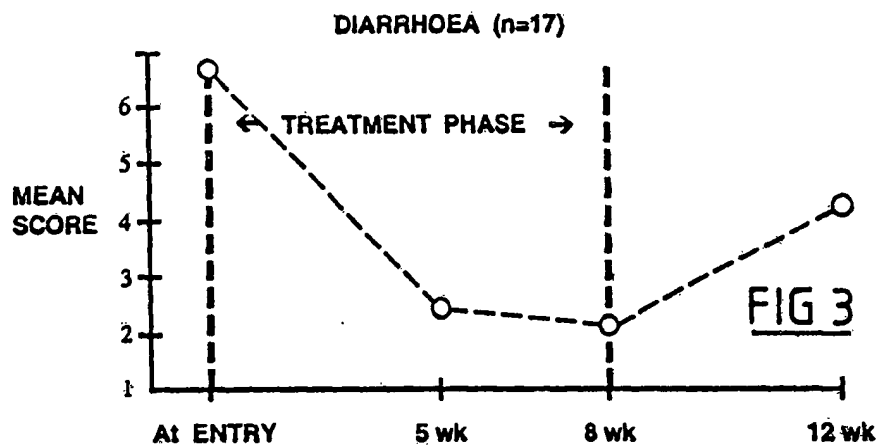
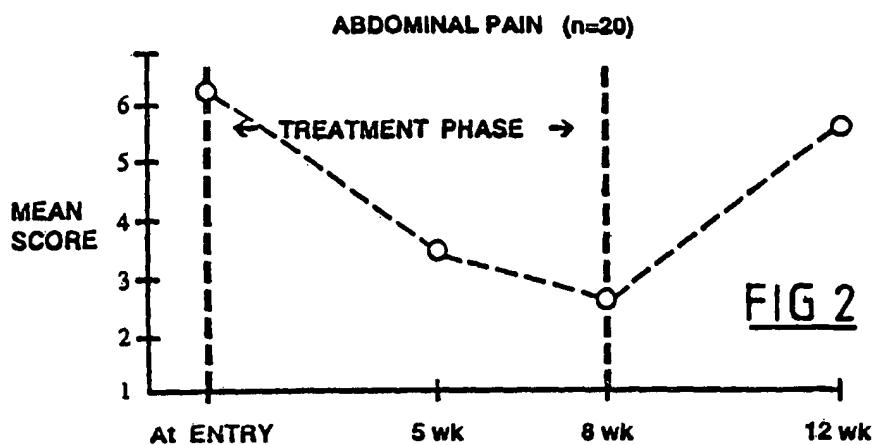
CARTER SMITH & BEADLE
Patent Attorneys for the Applicant:
THOMAS JULIUS BORODY

PATIENT CHARACTERISTICS

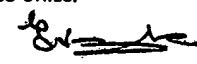
NO.	AGE	SEX	SYMPTOM SEVERITY SCORES AT ENTRY					DURATION (YEARS)
			PAIN	BLOATING	DIARRHOEA	CONSTIPATION	FLATULENCE	
1	36	F	5	6	-	7	-	6
2	33	F	7	-	-	7	-	5
3	26	F	4	6	-	7	-	5
4	60	F	7	4	6	-	3	15
5	42	F	7	-	6	6	4	9
6	33	F	7	4	6	7	-	5
7	37	F	-	-	8	-	3	6
8	30	F	6	-	6	-	-	10
9	48	F	7	-	-	7	3	15
10	38	F	6	8	8	-	6	7
11	44	F	8	7	7	-	-	6
12	45	F	3	4	9	-	-	10
13	39	F	2	4	9	-	3	7
14	24	F	-	3	6	5	-	3
15	56	F	6	4	7	-	3	15
16	37	M	5	-	7	-	5	7
17	45	M	6	-	9	-	-	10
18	36	M	8	-	6	-	-	5
19	59	M	7	3	-	7	3	15
20	74	M	-	-	-	6	-	35
21	68	M	9	-	8	-	7	20
22	51	M	7	-	3	-	5	8
23	59	M	8	5	4	2	6	10
	44.3y	15/8	87%	52%	74%	43%	52%	10.2yrs

* Percentage frequency of symptoms in the cohort

FIG 1



INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent classification (IPC) or to both National Classification and IPC Int. Cl. ⁸ A61K 031/60, 031/615, 031/625		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC	A61K 031/60, 031/615, 031/625	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸		
AU:IPC AS ABOVE		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category [*]	Citation of Document, ¹¹ with indication, where appropriate of the relevant passages ¹²	Relevant to Claim No ¹³
<input checked="" type="checkbox"/> X Y	WO, A, 81/02672 (FARMACEUTISK LABORATORIUM FERRING A/S) 1 October 1981 (01.10.81) See page 1	<u>1, 8, 12</u> 2-7, 9-11, 13-18
<input checked="" type="checkbox"/> X Y	WO, A, 81/02671 (FARMACEUTISK LABORATORIUM FERRING A/S) 1 October 1981 (01.10.81) See page 1	<u>1, 8, 12</u> 2-7, 9-11, 13-18
<input checked="" type="checkbox"/> PX PY	AU, A, 53672/90 (SMITH KLINE & FRENCH LABORATORIES LTD) 1 November 1990 (01.11.90) See page 1a	<u>1, 8, 12</u> 2, 7, 9-11, 13-18
<input checked="" type="checkbox"/> X Y	US, A, 4 664 256 (HALSKOV) 12 May 1987 (12.05.87) Column 1 (continued)	<u>1, 8, 12</u> 2-7, 9-11, 13-18
<p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" Document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to art oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 23 January 1992 (23.01.92)		Date of Mailing of this International Search Report 5 February 92 (05.02.92)
International Searching Authority AUSTRALIAN PATENT OFFICE		Signature of Authorized Officer T NIZNIK 

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

<input checked="" type="checkbox"/> Y	Biochemical Pharmacology, Volume 35, No. 2 issued 1986 (Great Britain) Roediger W et al, 'Effect of 5-amino salicylic acid (5-ASA) and other salicylates on Short Chain Fat Metabolism in Colonic Mucosa see pages 221-225	<u>1, 8, 12</u> 2-7, 9-11, 13-18
<input checked="" type="checkbox"/> Y	Biochemical Pharmacology, Vol 38, No 1, issued 1989 (Great Britain), Williams J G and Hallett, M B 'The Reaction of 5-Amino-Salicylic Acid Hypochlorite' see pages 149-154	<u>1, 8, 12</u> 2-7, 9-11, 13-18
<input checked="" type="checkbox"/> Y	Mims Annual 1989, 13th Edition by IMS Publishing (Australia) see pages 1-23	<u>1, 8, 12</u> 2-7, 9-11, 13-18
<input checked="" type="checkbox"/> Y	The Merck Index 1989, 11th Edition by Merck & Co Inc (USA) see page 1411 Drug No. 8917	<u>1, 8, 12</u> 2-7, 9-11, 13-18

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4a

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 91/00482

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member		
WO	81/02672			
WO	81/02671	US 4496553 US 5013727 US 4960765	US 4880794 US 5041431	US 4980173 CA 1222459
AU	53672/90	CA 2014889 JP 2295928	EP 3935329 NZ 233415	GB 8909559 PT 93884
US	4664256	CA 1230056	US 4664256	

END OF ANNEX